

CLAIMS

1. Mixed ester of hyaluronic acid wherein hydroxyl groups of hyaluronic acid are partially esterified with retinoic acid and butyric acid molecules, characterized in that the ratio between the degree of substitution with butyric acid and the degree of substitution with retinoic acid is at least 6.
2. The ester according to claim 1, wherein said ratio is at least 10.
3. The ester according to claims 1-2 wherein the degree of substitution with butyric acid ranges between 0.05 and 1.0 and the degree of substitution with retinoic acid ranges from 0.002 to 0.1.
4. The ester according to claim 3 where the degree of substitution with butyric acid ranges between 0.1 and 0.35 and the degree of substitution with retinoic acid ranges between 0.01 and 0.05.
5. The ester according to claim 1, wherein the average molecular weight (MW) of hyaluronic acid ranges from 10,000 to 30,000 Da.
6. The ester according to claims 1-5, for use in therapy.
7. The process for preparation of the esters described according to claims 1-6, wherein the esterification step with retinoic acid is carried out before the esterification with butyric acid derivatives.
8. The process according to claim 7 comprising the following steps:
 - i) formation of an alcoholate of hyaluronic acid;
 - ii) esterification of the alcoholate obtained in i) with retinoic acid derivatives to obtain a retinoic monoester of hyaluronic acid ;
 - iii) esterification of the monoester obtained in ii) with butyric acid derivatives to obtain the aforesaid mixed ester of hyaluronic acid.
9. The process according to claim 8, wherein the hyaluronic acid is used as a quaternary ammonium salt.
10. The process according to claim 8, wherein in step i) the pH of the reaction environment is at least 13.
11. The process according to claims 7-10, wherein the esterification reaction according to step ii) of the process is carried out using retinoyl chloride as esterifying agent.
12. The process according to claims 7-11, wherein the esterification

reaction as in point iii) is carried out using butyric anhydride as esterifying agent.

13. The mixed ester of hyaluronic acid carrying both a cytostatic and a pro-differentiating activity obtainable according to the process of claims 7 -12.

5 14. Pharmaceutical composition, carrying as the active principle at least one of the esters according to claims 1-6 or 13 in combination with pharmacologically acceptable excipients and/or diluents.

15. Pharmaceutical composition according to claim 14, in form of solution, suspension, soluble powder, granule, soft or rigid capsule, micro-capsule,
10 tablet, coated tablet, suppositories, ovuli, ointment, gel.

16. Use of the mixed ester of hyaluronic acid according to claims 1-6, for preparation of a medicament with anti-proliferative and pro-differentiating activity.

17. Use according to claim 16, wherein said medicament is active on solid tumors.

18. Use according to claim 16, wherein said medicament is active on systemic
15 tumors.

19. Use according to claim 18, wherein said systemic tumors are acute leukemia, acute promyelocytic leukemia, lymphomas, histiocytomas.

20. Use of the mixed ester according to claims 1-6 and 13 to induce the re-expression of surface antigens CD11a and CD11b.

20 21. An antiproliferative therapeutic method to a subject in need of an antiproliferative and prodifferentiating treatment, comprising administering to said subject a therapeutically effective amount of the mixed esters of the invention at therapeutically active doses.

25 22. An antitumoral therapeutic method to a subject in need of an antiproliferative and a prodifferentiating treatment, comprising administering to said subject a therapeutically effective amount of the mixed esters of the invention at therapeutically active doses.